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Ileal transposition: A non-restrictive bariatric surgical procedure that reduces body fat and increases ingestion-related energy expenditure

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ABSTRACT

Background: Ileal Transposition (IT) was developed as a model to study body weight reduction without the restrictive or malabsorptive aspects of other bariatric surgeries, but the exact mechanisms of the alterations in body weight after IT are not completely understood.
Objective: To provide a detailed description of the surgical procedure of IT, and describe its effect on energy balance parameters.
Methods: Adult male Lewis rats underwent either IT (IT+) or sham (IT-) surgery. Following surgery body weight and energy intake were monitored. After attaining weight stability (> 30 days), energy expenditure and its components were assessed using indirect calorimetry at a day of fasting, limited intake, and ad libitum intake. At the end of the study body composition analysis was performed.
Results: IT+ resulted in transiently reduced energy intake, increased ingestion-related energy expenditure (IEE) and decreased body and adipose tissue weight when compared to IT-. At weight stability, neither energy budget (i.e., energy intake - energy expenditure), nor energy efficiency was different in IT+ rats compared to IT-.
Conclusion: Our data show that the primary cause of weight reduction following IT+ is a transient reduction in energy intake. If the increased IEE is related to a higher level of satiety, compensatory feeding to bridge body weight difference between IT+ and IT- rats is less likely to occur.

1. Introduction

The rate of obesity, clinically defined as a body mass index (BMI) of 30 kg/m^2 or more [1], is on the increase causing or exacerbating a large number of health problems, both independently and in association with other diseases [2–4]. Even modest weight loss can significantly reduce morbidity and mortality induced by diabetes and cardiovascular conditions [5,6]. Medical programs developed several noninvasive options to lose and maintain adequate body weight, which are not always successful mainly because the weight loss is hard to sustain [3,5].

Gastrointestinal surgery is the only treatment shown to achieve long-term weight loss and therefore decrease the incidence of weight related diseases [7–10]. Historically bariatric surgeries used to be divided into two major classes: (1) mechanical reduction of the volume capacitance of the proximal stomach (gastroplasty surgeries) and (2) partial selective malabsorption procedures (jejunoileal bypass, biliopancreatic diversion). With the newer surgical methods where gastric restriction is combined with bypassing the proximal small intestine the question emerged which factor is responsible for the weight reducing effect of these surgeries: gastric restriction or the anatomical rearrangement of the small intestine. To investigate this question, ileal transposition (IT) was developed by Koopmans et al in 1981 [11]. In IT a segment of the lower ileum (10 cm from the ileocecal valve) is transposed distal to the duodenum, keeping the original length of gastrointestinal tract intact, without the confounding factors of gastric restriction and bypassing sections of the small intestine, and without malabsorption [11,12] that often coincides with restrictive surgeries. Therefore, the reduction of food intake and body weight are presumably solely due to ileal over-stimulation, which may lead to an enhanced ileal break. The ileal brake is a complex negative feedback mechanism of the gastrointestinal tract, originating from the stimulated ileal segment; resulting in the activation of neural and endocrine

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mechanisms that lead to delayed gastric emptying, gastrointestinal transit, secretion of gut hormones, and satiety [13–15].

Since the introduction of IT, a number of studies have been carried out using this model with modification in surgical techniques and methods such as different lengths of the transposed segments, various locations of the transections and using different suture techniques [16–19]. In this study we provide a detailed description of the original IT model by Koopmans, and describe its effects on energy balance in male rats that were feeding a balanced liquid diet, with equal proportions of macronutrients.

2. Material and methods

2.1. Animals and housing

All protocols were in accordance with the Canadian Animal Care guidelines and were approved by the University of Calgary, Animal Resource Care Centre. Twenty male Lewis rats (range: 288–328 g, mean weight 309 g) were singly housed in cylindrical transparent plastic cages (height: 50 cm, diameter: 33 cm) with rat chow and water allowed *ad libitum*, under artificial lighting (6am – 6pm) at room temperature. After 2–4 days of acclimatization, the rats were divided into two weight matched groups and fed with a liquid diet (4.184 kJ/gram). To prevent protein depletion [20,21] and micronutrient deficiency [20,22] sometimes observed in patients after bariatric surgery, rats received a diet consisting of a relatively high energy percentage of protein of 33%, with 33% carbohydrate, and 33% fat. Ingredients of the diet were Ensure High Protein with added protein (Resource Beneprotein instant protein powder, Novartis Medical Nutrition, USA) fat (Intralipid 20% IV infusion, Fresenius Kabi Clayton L.P., Clayton, NC) and adequate vitamins and minerals (Maltlevol liquid multivitamin, Carter-Horner Corp Mississauga ON, Canada), and this mixture was provided in glass jars. Animals were weighed daily at 3:30 pm and fed at 4:00 pm (resp. 2.5 and 2 h before lights off), and were allowed to consume as much diet as they wanted till the next morning at 9:00 am (i.e., 3 h after lights on). The diet jars were weighed before and after feeding intervals. Energy efficiency was calculated by the following equation:

$$\text{Energy efficiency} = \Delta\,\text{Bodyweight (kg) per day/average daily energy intake (kJ)}.$$

2.2. Surgical procedure

After overnight fast, rats were anaesthetized with ether, and the skin and muscle layer of the belly were cut at the midline exposing the abdomen. The small intestine was then transected at the level of (1) the duodenum 1 to 2 cm below the common bile and pancreatic duct, (2) the ileum at 10 cm from the ileocecal valve, and (3) the ileum 10 cm above this transection, creating an isolated 10 cm ileal segment. For the ileal transposition surgery, the 10 cm ileal segment was connected (using 6-0 Ethicon silk sutures) to the transected ends of the duodenum in the original direction of flow keeping its mesenteric blood supply and extrinsic innervation intact. The remaining ends of the ileum were sutured together, resulting in a gastrointestinal tract which had its original length without any excluded parts. For the control surgery, all transections were re-anastomosed in their original order. Postoperative care was given, by (1) a heating pillow underneath their home cage, (2) administration of Gentamicin (i.p. 37 μl/100 g bodyweight, 40 mg/ml, Sabex Inc Boucherville QC) and (3) butorphanol tartrate; (i.p. 0.2 mg/100 g bodyweight, 10 mg/ml, Wyeth Canada Guelph, ON). For the extensive description of the surgical procedure see supplementary data.

2.3. Energy expenditure measurement

Starting on the 33rd day after surgery, rats underwent indirect calorimetry measurements for analysis of energy expenditure (EE) using an Oxymax Analyzing System (Columbus Instruments, Columbus, OH) over the course of 3 consecutive days, for 23 h per day (i.e., from 2 h before lights off, till 3 h before lights off on the next day). To this end, rats were put in air-tight cages (diameter: 33 cm height: 50 cm), with wood shavings from their home cage, and with an airflow of 2.5 l/min. Every 10 min, air samples were taken from the outgoing airflow, and after drying were analyzed for O2 and CO2 concentrations, and these levels were compared to the O2 and CO2 levels measured in the dried samples of inflowing air. Differences in these concentrations yielded the rat's O2 consumption and CO2 production. O2 and CO2 sensors were calibrated daily with a standard gas mixture of 20.55% O2 and 0.490% CO2. EE was assessed on the basis of the equation of Lusk [23] and Ferranninni [24].

Before the start of the indirect calorimetry measurements, rats had one day of habituation with ad libitum food available in the indirect calorimetry system. On the next day, food was not returned at the time they expected it (i.e., 2 h before lights off), and rats subsequently underwent a day of fasting. Consequently, the measurement of energy expenditure on the fasting day established a baseline of daily total energy expenditure (TEE) and its components, resting metabolic rate (RMR) and non-exercise activity thermogenesis (NEAT). RMR was calculated by taking the mean of the four lowest levels of 10 min energy expenditures in the indirect calorimetry system (usually found at the middle of the light phase, and this usually coincided with sleeping behavior as assessed by visual inspection). Extrapolating this towards the whole day (thus multiplying the mean of energy expenditure over 10 min by 144), gave us an estimation of daily RMR. Finally, NEAT was calculated by subtracting RMR from TEE.

During the following day in the indirect calorimeter rats received a jar filled with exactly 251 kJ of their habitual diet (i.e., at 2 h before lights off), which was slightly below their normal intake to ensure that all rats ate an equal amount of food. Complete intake of this 251 kJ was verified at the end of the limited intake day. This standardized intake allowed us to assess ingestion-related energy expenditure (IEE), by calculating the temporal increase of TEE on the limited intake day above the level of TEE on the fasting day. For completeness, also RMR and NEAT were calculated on the limited intake day. Calculating IEE on the limited intake day as a percentage of the known daily total energy intake (TEI) on the limited intake day allowed us to calculate the specific dynamic action (SDA) of ingested nutrients for each rat [23]. This calculated SDA for each rat is an approximation of the energy expenditure effect of any amount of energy ingested, and thus also could be used to approximate IEE under ad libitum conditions, which took place during the third day of indirect calorimetry. Consequently, on the third day, ad libitum energy intake was reinstated and assessed, and TEE, RMR, IEE and NEAT were calculated for the ad libitum intake day. Energy budget was calculated by subtracting TEE from TEI based on the calculations of both feeding days (limited and ad libitum day).

2.4. Sacrifice

Animals were sacrificed by decapitation under light ether anesthesia on day 45. The gastrointestinal tract was removed and the following segments were obtained and weighed: stomach, upper duodenum (from the pylorus to the pancreatic duct), lower duodenum (from the pancreatic duct to the ligament of Treitz), jejuno-ileum, transposed segment and last 10 cm of ileum, cecum and colon together.

To evaluate body composition we carefully separated all abdominal and subcutaneous adipose tissue pads from lean mass, and measured the wet weight of lean body mass (LBM) and of the various adipose tissue pads. This means that we did not include intramuscular or intraorgan fat as being part of "adipose mass". Furthermore, skin and organs with high energy expenditure rate (i.e., heart, liver, kidneys, brain, spleen) were weighed separately too.

2.5. Statistical analyses

Comparisons between the two groups were performed with a repeated measures ANOVA for the daily body weight and energy intake. Energy expenditure data were analyzed using t-tests and ANCOVAs (with lean body mass, fat mass, and total body weight as co-variates of body size) to assess differences of mass-specific metabolic rates [25]. Data is presented as mean ± se and p values less than 0.05 were considered significant.

From the IT+ group two animals died, one because of inadequate sutures at the most distal anastomosis site, and the other animal lost weight rapidly and did not reach any weight regain without visible surgical cause. From the IT- group one rat died before the end of the experiment and therefore excluded from all analysis (IT+, $n = 8$, IT-, $n = 9$). In addition, one IT+ rat and one IT- rat had a failing energy expenditure measurement on the ad libitum day, and therefore could not be used for analysis of the ad libitum day energy expenditure assessments.

3. Results

3.1. Body weight and energy intake

Average pre-surgery body weights of IT- and IT+ rats were similar (IT-: 339.8 ± 10.7 g, IT+: 337.9 ± 7.0 g). Repeated measures ANOVA revealed a significant interaction of body weight with time ($F(30,450) = 3.511$, $p < 0.0001$), with body weights in the IT+ group being significantly lower than in the IT- group after surgery (Fig. 1A). The weight gap increased with the number of days postsurgical, which then reached the level of significance on day 13 ($p < 0.05$) and continued to increase (from day 28 $p < 0.01$, from day 36 $p < 0.001$), and then somewhat decreased and stabilized (day 39 $p < 0.01$, day 42 $p < 0.05$; Fig. 1A). Recovery period was defined as the number of days when animals reached their lowest body weight. IT- had significantly shorter recovery period (5.0 ± 0.5 days vs 7.8 ± 0.5 days, $p < 0.05$) than IT+ rats but lost almost as much weight (46.8 ± 1.0 g and 46.8 ± 3.7 g, respectively). At the end of the 45 days IT- rats weighed significantly more (359.4 ± 5.0 g) than IT+ (337.9 ± 8.1 g) ($p < 0.05$).

Average pre-surgery energy intakes of IT- and IT+ rats were similar (IT-:355.5 ± 23.38 kJ, IT+: 350.8 ± 23.41 kJ). Repeated measures ANOVA did not detect an effect of surgery on energy intake (Fig. 1B). However, calculating cumulative intake over 10-day periods showed that IT+ significantly reduced food intake during the second 10 day-period ($F(1, 15) = 1.956$; $p < 0.05$) following surgery (Fig. 1C).

3.2. Energy expenditure

During the fasting day, no differences in TEE, RMR and NEAT were seen between IT+ and IT- rats (Fig. 2A). This effect did not change when an ANCOVA was performed which controlled for co-variates of body size (i.e., LBM, adipose tissue mass, and/or total body weight). Subtraction of TEE on the fasting day from TEE on the limited intake day yielded a proxy for IEE during the limited intake day (Fig. 2B) upon eating the fixed 251 kJ of diet. The concomitant SDA values (3.15 in IT- rats versus 9.14 in IT+ rats; ($F(1,15) = 7.439$, $p < 0.05$) as well as IEE on the limited intake day ($F(1,15) = 7.674$, $p < 0.05$) were significantly higher in the IT+ rats than in the IT- rats. SDA values allowed us to calculate the levels of IEE on the ad libitum day, and IEE was elevated in IT+ rats versus IT- rats on the ad libitum day too ($F(1,13) = 6.444$, $p < 0.05$; Fig 2C). When body size correlates were used as co-variates in an ANCOVA, IT+ rats again had higher IEE on the limited intake day and ad libitum intake day (for LBM: resp.; $F(1,14) = 5.613$, $p < 0.05$, and $F(1,12) = 5.645$, $p = 0.05$) relative to the IT- rats (Fig. 2B and C).

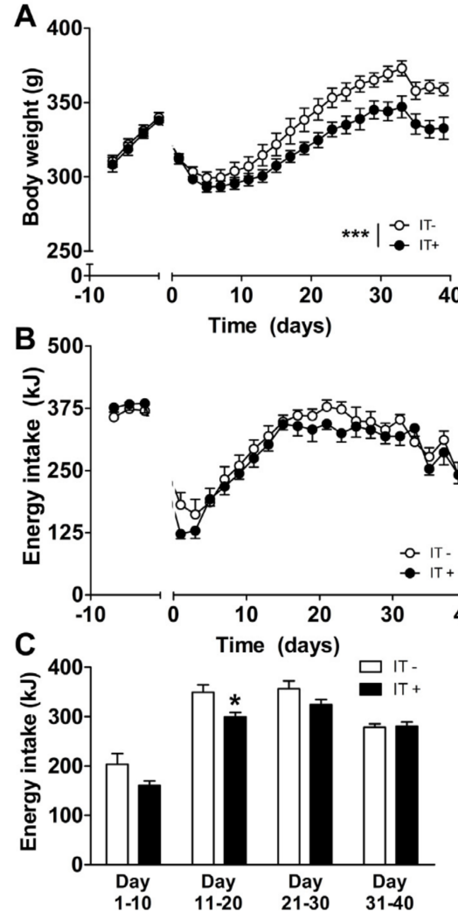

Fig. 1. Body weight (A), energy intake (B), and 10-day cumulative energy intake (C) before and after ileal transposition (IT+) and control surgery (IT-). Averages are given ± SEM. Differences between IT + and IT- are indicated by * ($p < 0.05$).

Levels of NEAT were significantly reduced in IT+ rats versus IT – rats on the limited intake day ($F(1,15) = 5.027$, $p < 0.05$) and ad libitum day ($F(1,13) = 5.369$, $p < 0.05$) (Fig. 2B and C). These differences were lost in an ANCOVA with all correlates (i.e., LBM, adipose tissue mass and/or total body weight) as co-variates. TEE during the limited intake and ad libitum days were not different between IT+ and IT- rats, either with or without co-variates of body size.

3.3. Energy budget and efficiency

Energy budgets of IT+ and IT- rats (Fig. 3A) were not different. Also energy efficiency calculated during the post-operative period of day 20 till day 40 did not differ between the IT+ and IT- rats (Fig. 3B).

3.4. Body composition

Although body weight of IT+ rats was significantly lower than that of IT- at the time of sacrifice ($p < 0.01$) their lean body mass did not differ significantly (see Table 1). The small and the large intestines and the pancreas were significantly enlarged in IT+ rats ($p < 0.01$-$p < 0,0001$), the other organs and muscle mass were not affected by surgery. IT+ rats had significantly less adipose tissue than the IT- did (several depots $p < 0.01$–$p < 0.0001$).

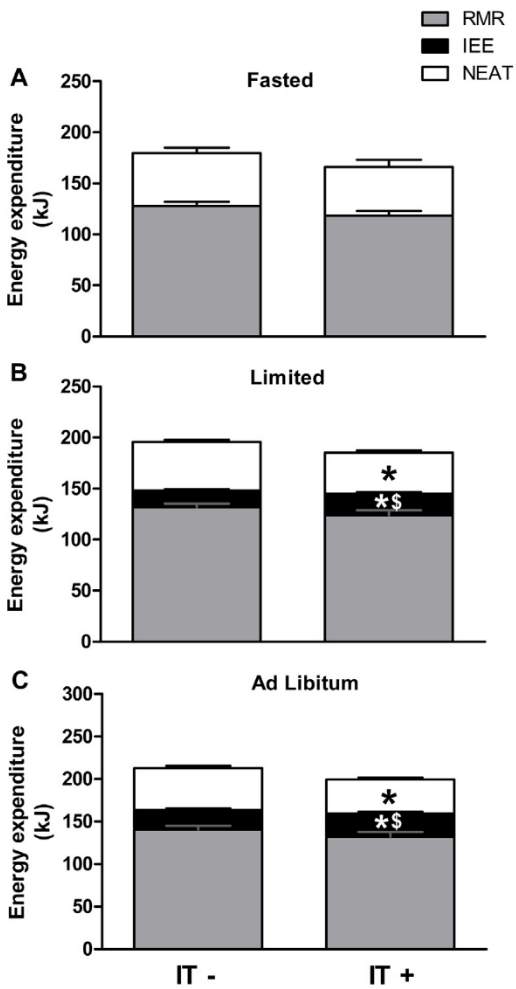

Fig. 2. Total daily energy expenditure (kJ), and its constituents resting metabolic rate (RMR), ingestion-related energy expenditure (IEE), and non-exercise activity thermogenesis (NEAT) expressed for ileal transposed rats (IT+) or their sham operated controls (IT-). This is shown for a day of fasting (A), during a limited intake day (B) and ad libitum intake day (C). Statistical difference is indicated by * ($p < 0.05$), and by $ ($p = 0.05$) when corrected for lean body mass using ANCOVA.

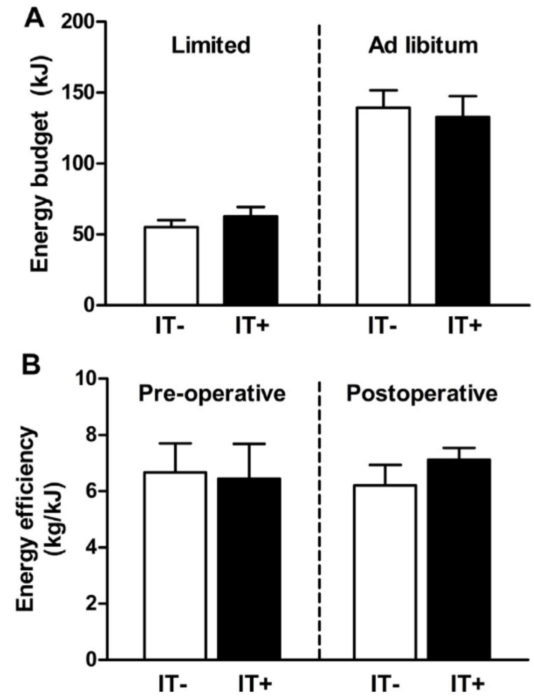

Fig. 3. Energy budget (A; i.e., energy intake – energy expenditure) in limited intake (left panel) and ad libitum (right panel) conditions. Energy efficiency (B; i.e., Δ body weight (kg)/energy intake (kJ) in the pre-operative (left panel) and postoperative (right panel) phase.

Table 1
The wet weight of different organs (in grams) at the time of sacrifice.

Surgery	IT-	IT+	Significance
Body weight (g)	392.66 ± 3.87	360.21 ± 11.36	<0.01
Total gut with content (g)	25.01 ± 0.47	30.52 ± 0.88	<0.0001
Stomach (g)	1.20 ± 0.02	1.28 ± 0.04	ns
Duodenum (g)	0.52 ± 0.04	0.82 ± 0.05	<0.0001
Transposed segment (g)	0.44 ± 0.04	1.76 ± 0.19	<0.0001
Jejeno-ileum (g)	2.18 ± 0.14	3.39 ± 0.41	<0.0001
Last 10 cm of ileum (g)	0.35 ± 0.03	0.50 ± 0.04	<0.01
Cecum + colon with content (g)	4.63 ± 0.30	6.19 ± 0.41	<0.01
Pancreas (g)	1.31 ± 0.04	1.61 ± 0.04	<0.0001
Spleen (g)	0.76 ± 0.07	0.81 ± 0.06	ns
Liver (g)	13.57 ± 0.21	13.73 ± 0.42	ns
Kidneys (g)	2.67 ± 0.02	2.53 ± 0.10	ns
Heart (g)	1.02 ± 0.02	1.00 ± 0.03	ns
M. gastrocnemius (g)	2.15 ± 0.03	2.01 ± 0.08	ns
Mesenteric fat (g)	6.13 ± 0.29	4.76 ± 0.59	<0.05
Omental fat (g)	1.62 ± 0.10	1.20 ± 0.17	<0.05
Epididymal fat (g)	5.51 ± 0.38	4.68 ± 0.57	ns
Retroperitoneal fat (g)	10.72 ± 0.61	6.36 ± 0.90	<0.001
Subcutaneous fat (g)	19.11 ± 1.60	13.02 ± 1.72	<0.05
Visceral fat (g)	7.75 ± 0.36	5.96 ± 0.73	<0.05
Abdominal fat (g)	19.24 ± 1.02	13.05 ± 1.60	<0.01
Inguinal fat (g)	7.66 ± 0.82	5.64 ± 0.88	ns
BAT (g)	0.33 ± 0.05	0.26 ± 0.03	ns
LBM (g)	303.90 ± 1.46	297.64 ± 5.94	ns

4. Discussion

We present here a detailed description and analysis of the original Koopmans' model of ileal transposition with a survival percentage of 80%, which is comparable to other studies (survival percentage between ~70–100%) [11,17]. Overall, ileal transposition caused changes in energy balance parameters, as shown by reduced energy intake and increased ingestion-related energy expenditure (IEE). Furthermore, we showed weight loss and reductions in fat content in IT+ rats compared to IT- rats without differences in energy budget and energy efficiency after the recovery period. Important for consideration of these results is the fact that the control (IT-) rats had exactly the same transections and tissue dissections, ruling out factors beyond the transposition itself.

After initial body weight loss following surgery, body weight recovered to pre-operative values after ~30 days, with higher weights of IT- rats versus IT+ rats at the end of the experiment. Initial cumulative energy intake of the IT+ rats was lower than that of the IT- rats lasting for ~10 days (assessed by 10-day cumulative blocks of energy intake measurements). Our findings that energy intake, energy budget and energy efficiency did not differ between IT+ and IT- animals at the final stage of the study may indicate that the acquired differences in body weight between IT+ and IT- rats were rather stable. These results are comparable to findings by others published previously [11,17], although there are also findings that IT does reduce energy efficiency [16]. Differences in study design and type of diet may be responsible for inconsistencies between studies.

In the present study, we observed that non-exercise activity thermogenesis (NEAT) was significantly lower in the IT+ rats compared to the IT- rats during the limited intake and ad libitum day. At first, this seems to indicate that rats that underwent IT spare energy, perhaps as a response to reduced fat storage in the IT+ relative to the IT- rats.

However, because the IT+ rats had smaller body weight relative to IT- rats, components of energy expenditure at the time of measurement may be the same in IT+ and IT- rats when corrected for body size (and/or correlates hereof). For this reason, we performed ANCOVAs with lean body mass, adipose tissue mass, and total body weight as co-variates of body size and observed that differences in NEAT were lost. While our body composition analysis included wet weight assessment of adipose tissue weights and lean body mass at the end of the study in an ad libitum condition (i.e., thus ignoring potential differences in body weight compartments between fasted and fed states), our data seem to indicate that the mass-specific NEAT was not different between groups. At this point, we cannot exclude the possibility that differences in TEE, NEAT, and/or RMR did exist in an earlier phase after IT where differences in body fat content started to materialize.

In contrast, ingestion-related energy expenditure (IEE) was elevated in the IT+ rats versus IT- rats, and these effects persisted when we included afore mentioned co-variates for body size, in particular LBM, in the analysis. Sub-components of IEE are diet-induced thermogenesis (DIT) and the energy expenditure associated with digestion, transport and storage of nutrients [26]. Also differences in physical activity could contribute to differences in IEE, however, we did not have the opportunity to actually assess this in the indirect calorimetry system. It may be speculated that the transposed segment augments hormone mediated increases in DIT, for example via increased release of GLP-1, which has been shown to increase BAT thermogenesis via increased sympathetic activity [27], although controversy exists regarding this point [28].

It may be speculated that the expedited delivery of nutrients into the transposed segment activated an exaggerated ileal brake, with higher levels of energy expenditure associated with digestion, processing, and storage of the ingested nutrient. Increased sympathetic activity may play a role in this process [29]. Additionally, anatomical adaptation following IT (such as hypertrophy of the gut) may have contributed to the changes in IEE as well. Increased IEE may be related to increased satiety [30] and/or reduced hunger [31], which could mechanistically be linked via elevated feeding-related levels in PYY and GLP-1 induced by ileal transposition [32].

In our study, animals were feeding a diet with a relatively high content of protein and fat (mainly consisting of oils), relative to the macronutrient composition of regular lab chow diets. It is known that a high protein diet results in early and prolonged satiation [33,34] and promotes fat loss [35]. A diet high in polyunsaturated and monounsaturated fats also reduces weight gain [36,37] and increases satiety if lipids reach the ileum undigested (emulsified) [38,39]. It is probable that both the satiating effect of high protein content and the stronger ileal brake by the high fat content of the diet we used could have masked some aspects of ileal transposition. It is therefore of importance to keep in mind that, although bariatric surgery may have positive effects on muscle mass [40], the finding that LBM was not affected by ileal transposition could also be a reflection of a diet with an elevated, but not too high, protein content. There are certainly conditions of surgery-induced sarcopenia, with maladaptive consequences for sustainable health [41,42].

In the present study, we used lean rats, and it would certainly be of interest to investigate whether the findings and the abovementioned mechanisms would also apply to dietary obese or genetically obese rats that underwent ileal transposition. It also needs to be taken into account that the transposed segment was disconnected from the enteric nervous system in the IT+ as well as the IT- rats, which probably altered relaying of enteroendocrine cell-mediate nutrition related information [43]. Thus, although IT- and IT+ rats had equal enteric disconnections, it may have masked some of the effects of transposition as also the enteric disconnected segment in IT- rats may have sensed intestinal distension differently (if at all), which could potentially affect food intake [44]. Finally, although proper perfusion of (non)transposed ileal segments was confirmed in a pilot experiment, we do not know to what extent this may have differed, and affected the outcomes in rats in the present study.

In summary, we show a detailed description of the surgical procedure of ileal transposition, which caused body weight loss and a transiently decreased energy intake. Energy budget and energy efficiency did not differ between IT+ and IT- animals. Energy expenditure analysis showed that mass-specific metabolic rates were similar for most components of energy expenditure, except for ingestion-related energy expenditure (IEE). This suggests that after IT+, the transposed segment augments (hormone/food- mediated increases in) thermogenic efficacy and/or energy-costly aspects of digestion, transport and/or storage of nutrients. If the increased IEE is related to a higher level of satiety, compensatory feeding to bridge body weight difference between IT+ and IT- rats is less likely to occur.

Declaration of Competing Interest

None

Acknowledgment

Professor Henry Koopmans was one of the first researchers who used ileal transposition as a model to investigate the gut aspect of the regulation of food intake, weight control and appetite and aimed to shed light how these mechanisms can be used in the treatment of obesity. I (ES) feel privileged to count myself one of his pupils who could learn the technique directly from him. Professor Koopmans left a legacy which is still alive, even more, ileal transposition now is used in combination with other surgical techniques in human bariatric surgeries. This work was performed in the laboratory of – and supported by – HSK, as well as in the laboratory of – and supported by - GvD.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.physbeh.2020.112844.

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